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**Medical Science**

# Is there a role for probiotics in prevention and treatment of allergic diseases in children? – review of literature

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## ABSTRACT

Allergic diseases in the pediatric population are a significant burden to healthcare systems, families, and children themselves. They decrease patients' quality of life. Some allergic conditions are life-threatening. Therefore, it is vital to investigate new pathways that could facilitate their treatment and prevention. This review gathers information from recent studies regarding probiotics as an additive therapy in allergic bronchial asthma, atopic dermatitis, allergic rhinitis, and food allergy. In light of the increasing prevalence of atopic diseases among children worldwide the "Hygiene hypothesis" gained interest among scientists. It associates the rising incidence of allergies with limited exposure to the natural environment and infectious diseases in early childhood. This absence of immune stimulation presumably causes immunity dysregulation and hyperresponsiveness, resulting in atopy. Probiotics supplementation, aiming to enrich the gut microbiota, has become a field of research. There is hope that a more diverse and abundant microbiome will result in immunity maturation and immunotolerance. Outcomes of conducted trials in the subject vary from apparent preventive or alleviating symptoms effect to no significant difference noted. The authors point out that there should be more research focused on single bacterial strains in a specific disease, precise dosage, and administration period. Overall, taking into account the latest reports, there are more and more studies that show the beneficial effects of probiotics on allergic diseases. However, there is not enough evidence to make recommendations regarding their routine use.

**Keywords:** Allergy; probiotics; hygiene; microbiota

## 1. INTRODUCTION

More and more people live in highly urbanized habitats nowadays (Garn et al., 2021; Haahtela, 2019). There are better living conditions, better hygiene, and more developed health care than in previous centuries. We can observe an increase in the prevalence of allergic diseases along with these changes (Haahtela, 2019; Fiuza et al., 2021; Depoorter and Vandenplas, 2021). In 1989, Strachan proposed the Hygiene Hypothesis, which states that many conditions associated with non-proper immunity functioning (such as asthma, allergic rhinitis, atopic dermatitis, and food allergy) might be the result of diminished exposure to pathogens and antigens from the natural environment (Pfefferle et al., 2021). New laboratory research techniques allowed to specify the mechanisms behind this concept (Garn et al., 2021).

Many research groups have shown that living in rural sites, exposure to unprocessed cow's milk, diverse vegetation pollen, barn dust, and soil among others has a protective effect on excessive immune response and allergies (Garn et al., 2021; Haahtela, 2019; Pfefferle et al., 2021; Von-Mutius, 2021). According to those studies, the gut microbiota, especially in early childhood, is crucial for the proper maturation of immunity (Mennini et al., 2017). An infant's gut colonization by symbiotic bacteria determines the development of immunotolerance and regulating processes (Depoorter and Vandenplas, 2021; Mennini et al., 2017). Intestinal dysbiosis reduces immune cells stimulation and leads to pathological allergic reactions (Garn et al., 2021; Drago et al., 2022). As a consequence of these reports, scientists began to analyze if probiotics as add-on therapy in atopic diseases could modulate the immunological response and further, alleviate the symptoms and improve the patient's quality of life (Mennini et al., 2017).

**Probiotics and allergic diseases**

Allergic diseases are common chronic disorders of developmental age (Depoorter and Vandenplas, 2021; Maciag and Phipatanakul, 2020). They burden the healthcare system (due to exacerbations requiring hospitalization) and affect children's social life through school absence and limited ability to perform the same activities as their peers (Drago et al., 2022; Maciag and Phipatanakul, 2020; Ciprandi and Tosca, 2022). These conditions derive from atopy, which is a predisposition to dysregulated, type-2 dominated immunological response typical of the fetus. It results in an excessive reaction to harmless factors, causing unnecessarily intensive production of immunoglobulin E (IgE) (Ciprandi and Tosca, 2022; Justiz-Vaillant et al., 2024). This pathology entails allergy symptoms such as mucosa swelling, nasal congestion, hypersensitivity of the bronchi, skin itching, and redness, diarrhea, and conjunctivitis.

Allergic bronchial asthma, allergic rhinitis, atopic dermatitis, and food allergy are the most frequent atopy manifestations (Justiz-Vaillant et al., 2024). The listed diseases have the same fundamental cause, but the pathways of disturbed immunological reactions may vary. There is a need for an individual approach considering the use of specific probiotic strains or strain combinations, dosage, and route of administration. Probiotics, by the World Health Organization definition, are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". Their main advantages are being accessible to purchase and perceived as safe. Unfortunately, most of the available products registered as food supplements do not undergo such thorough inspection as medicinal products (Depoorter and Vandenplas, 2021).

Therefore, we cannot be sure if what is on the label about the strains contained, their dosage, vitality, and bioavailability is accurate. Though the occurrence of adverse events is infrequent, some reports state an increased risk of endocarditis when administered to patients with a structural heart defect, d-lactic acidosis, and systemic infections in patients with compromised immunity (Depoorter and Vandenplas, 2021; Wang et al., 2019). In this regard, probiotics are not recommended in critically ill patients (Wang et al., 2019). Possible benefits and risks should be carefully taken into consideration before suggesting their use. Probiotic supplementation aims to restore intestinal homeostasis, induce adequate stimulation of immune cells, and obtain better immunotolerance (Mennini et al., 2017). It is essential to investigate the diseases separately to reveal specific strains that could benefit each condition.

**Aim**

This study aims to review the latest information regarding probiotics as an element of therapy and prevention of the most common allergic diseases in children.

## 2. METHODS

We conducted a thorough search of free access databases, including PubMed, Google Scholar, and the National Library of Medicine, using keywords such as “atopic diseases”, “allergy”, “probiotics”, “asthma”, “allergic rhinitis”, “atopic dermatitis”, and “food allergy”. These terms were exploited to distinguish relevant articles. Firstly, we screened articles based on their titles and subsequently analyzed their abstracts. We included scientific papers written in English with the publication date after 2016. Articles published before 2016 were excluded from further consideration. Only papers focusing on the use of probiotics in the prevention and treatment of allergic diseases were included in our study. We searched for the articles until 1st February 2024.

## 3. RESULTS AND DISCUSSION

**Allergic bronchial asthma**

Asthma is a chronic, non-communicable, respiratory disease (Maciag and Phipatanakul, 2020). Hypersensitivity of the bronchi leads to reversible airway obstruction (Justiz-Vaillant et al., 2024; Chabra and Gupta, 2024). Pro-inflammatory mediators released in reaction to harmless to healthy person factors cause symptoms (Justiz-Vaillant et al., 2024). Exposition to an allergen, stress, emotional upset, exercise, airborne pollutants, gastroesophageal reflux disease, or infection can provoke asthma exacerbations, which can be severe and lead to hospitalization (Chabra and Gupta, 2024). It is indisputable that the basis of treatment is medications like inhaled corticosteroids and long- and short-acting β2-agonists administered in proper amounts and combinations adequate to the severity of the illness Beasley et al., (2022), but what could we do to aid the therapy and achieve better results is a field of research.

Asthma is heterogeneous, and its occurrence is determined by genetic and environmental factors (Hufnagl et al., 2020). Protective factors that reduce the risk of developing the disease are exposition to a natural habitat, plants, and farm animals and avoiding pollution in early childhood (Garn et al., 2021; Haahtela, 2019; Pfefferle et al., 2021; Von-Mutius, 2021). Microbiota in the infant’s gut significantly affects proper immunity maturation. It is influenced negatively by cesarean section delivery, feeding a newborn with a milk formula instead of breastfeeding, and the use of antibiotics in the neonatal period (Hufnagl et al., 2020; Colquitt et al., 2022). Recently, lung bacterial diversity got the scientists’ interest. Research has shown that dysbiosis in this area could also influence susceptibility to developing asthma.

The new finding is the existence of the lung-gut axis. It has turned out that the gut microbiota affects the bacterial diversity of the lungs (Hufnagl et al., 2020). For this reason, it is hoped that the administration of probiotics could result in the enrichment of intestinal microbiota and its increased presence in the bronchi. Initially, the outcomes of pre-clinical studies supported the idea that exposing individuals to bacterial antigens and microbial metabolic products would diminish inflammation of the bronchial mucosa (Hufnagl et al., 2020). Encouraged scientists proceeded to broaden their knowledge in this scope; however, they moved the research interest to humans. In Ciprandi and Tosca, (2022) thoroughly reviewed the latest findings regarding the use of probiotics in children with asthma. Conclusions in mentioned systematic reviews and meta-analyses were inconsistent.

There are papers stating that supplementation alleviated symptoms and reduced the frequency of asthma exacerbations, as well as documents stating that there was no significant difference in symptom severity, bronchial function tests, and asthma prevalence when comparing children given probiotics with those in the placebo group. The authors highlighted that research should investigate specific bacterial strains instead of diverse probiotic mixtures (Ciprandi and Tosca, 2022). We have searched for trials regarding particular bacterial strains published in 2017-2024. Cabana et al., (2017) investigated, in a double-blind controlled trial, whether the administration of Lactobacillus rhamnosus GG (LGG) to high-risk infants for the first six months of life has an impact on the incidence of asthma.

Even though the study revealed 17.4% incidence in the control group and 9.7% in the probiotics group, the hazard ratio was not statistically significant (Cabana et al., 2017). Miraglia-Del-Giudice et al., (2017) revealed that pediatric patients with intermittent asthma given a Bifidobacteria mixture (B. longum BB536, B. breve M-16 V, and B. infantis M-63) demonstrated better quality of life than the placebo group. Huang et al., (2018) investigated 6-18 years of age children with at least a 1-year history of intermittent to moderate persistent asthma who received Lactobacillus paracasei GMNL-133 and Lactobacillus fermentum GM-090 both separately as well as their mixture and stated that this intervention mitigated the symptoms and enhanced asthma control.

Also, the mixture was more effective than Lactobacilli strains alone (Huang et al., 2018). The latest study considering specific probiotic strains was conducted by (Drago et al., 2022). This study, titled "The Probiotics in Pediatric Asthma Management (PROPAM)", was published in 2022. It describes randomized, placebo-controlled, and double-blind trials. Researchers evaluated the

mixture of Ligilactobacillus salivarius LS01 and Bifidobacterium breve B632 applied to children in primary care settings (Table 1). Outcomes have shown that this combination of strains significantly reduced the occurrence and severity of asthma exacerbations (Drago et al., 2022).

**Table 1** Studies on specific probiotic strains in allergic bronchial asthma

| Study | Year | Probiotic strains | Effects |
|---|---|---|---|
| Cabana et al., | 2017 | Lactobacillus rhamnosus GG | Nonsignificant |
| Miraglia-Del-Giudice et al., | 2017 | Bifidobacteria mixture (B. longum BB536, B. breve M-16 V, B. infantis M-63) | Better quality of life than the placebo group |
| Huang et al., | 2018 | Lactobacillus paracasei GMNL-133 (LP) and Lactobacillus fermentum GM-090 (LF) separately and their mixture | LP and LF can reduce asthma severity and improve asthma control in school-age children. The combination of LP plus LF appears to be more effective in childhood asthma than either LP or LF alone |
| Drago et al., | 2022 | Ligilactobacillus salivarius LS01 and Bifidobacterium breve B632 mixture | Significantly reduced occurrence and severity of asthma exacerbations |

In Colquitt et al., (2022) reviewed papers regarding the impact of probiotic supplementation by mothers during pregnancy on the development of atopic diseases in children. In the case of allergic asthma, the intervention had no significant effect on preventing asthma or wheeze (Colquitt et al., 2022).

**Allergic Rhinitis**

Another manifestation of atopy is allergic rhinitis (AR). Its prevalence ranges from 5-50% worldwide, but the differences may result from incoherence in diagnostic criteria. The highest incidence occurs among children and initial symptoms usually appear in school age (Wise et al., 2023). The pathophysiological mechanism of the disease is hyperresponsiveness of the nasopharyngeal mucosa to allergens, leading to inflammation, swelling, and watery secretion, which cause nasal congestion, rhinorrhea, sneezing, itching of the nose, and ocular symptoms such as conjunctivitis (Justiz-Vaillant et al., 2024). Those symptoms may not be as severe and life-threatening as bronchial asthma; still, they significantly decrease patients' quality of life and interfere with sleep quality and learning ability.

Thus, it is vital to search for new possibilities that could improve patients' comfort and health, except for antihistamines, nasal decongestants, topical glucocorticoids, and allergen-specific immunotherapy (Liu et al., 2022). In Liu et al., (2022) reviewed recent clinical studies regarding probiotics use in AR. Described papers revealed that Lactobacillus paracasei (LP-33) administered for six weeks to children with perennial AR resulted in significant improvement in baseline symptoms and the relieving effect was comparable to cetirizine (Ahmed et al., 2019). Another research group found that *Lactobacillus helveticus* LBT2171 (LH2171) supplementation diminished nasal symptoms and decreased eosinophil count in nasal fluid and peripheral blood in comparison to the placebo group - patients with mild to moderate AR (Yamashita et al., 2020).

The positive effect of probiotic use was also observed in studies involving probiotic mixtures (Table 2). A combination of bifidobacteria (*B. longum* BB536, B. infantis M-63, B. breve M-16V) improved patients' quality of life (Miraglia-Del-Giudice et al., 2017). *Bifidobacterium longum* IM55 and Lactobacillus plantarum IM76 Kang et al., (2020), *Bifidobacterium animalis* subsp. Lactis BB12 and *Enterococcus faecium* L3 Anania et al., (2021) mixtures investigations also gave positive results. Furthermore, scientists evaluated research focusing on probiotics in combination with budesonide, with sublingual immunomodulating treatment (SLIT) and SCIT and the results (Table 3) showed that adding probiotics as part of therapy was beneficial (Liu et al., 2022).

**Table 2** Studies on specific probiotic strains in allergic rhinitis

| Study | Year | Probiotic strain | Effects |
|---|---|---|---|
| Ahmed et al., | 2019 | *Lactobacillus paracasei* (LP-33) | Significant improvement in baseline symptoms and the relieving effect comparable to cetirizine in children with perennial AR |
| Yamashita et al., | 2020 | *Lactobacillus helveticus* LBT2171 (LH2171) | Supplementation diminished nasal symptoms and decreased eosinophil count in nasal fluid and peripheral blood in patients with mild to moderate AR |

**Table 3** Studies on probiotic mixtures in allergic rhinitis.

| Study | Year | Probiotic strains | Effect |
|---|---|---|---|
| Miraglia-Del-Giudice et al., | 2017 | B. longum BB536, B. infantis M-63, B. breve M-16V | Improved patients' quality of life and reduction of nasal symptoms |
| Kang et al., | 2020 | Bifidobacterium longum IM55, Lactobacillus plantarum IM76 | Alleviation of AR symptoms |
| Anania et al., | 2021 | Bifidobacterium animalis subsp. Lactis BB12, Enterococcus faecium L3 | Reduced incidence of AR symptoms and a reduction in medical conventional therapies in children and adolescents |

Capponi et al., (2022) wrote about a new idea: the administration of postbiotics and parabiotics to stimulate the immunological response. They described postbiotics as bacterial or metabolic products from microorganisms that are non-viable, but have biological activity in the host. Differently, probiotics are dead microbial cells (either intact or broken) or crude cell extracts, which, when administered in proper amounts, confer a benefit on the consumer. Research has shown that not only probiotics themselves but also their metabolites namely Shorty Chain Fatty Acids (SCFAs), bile acid-derived metabolites, microbial polysaccharides, indole-3-lactic acid (IDO), 12,13-diHOME, and the B6 and B3 vitamins balance immunological responses and have the anti-inflammatory effect, however, human clinical trials are needed to reveal if the impact of such intervention can be seen in patients (Capponi et al., 2022).

**Atopic Dermatitis**

Atopic dermatitis (AD) is a chronic or recurrent disease characterized by an impaired skin barrier, resulting in dry, scaly, and itchy skin, often accompanied by prurigo or erythematous lesions (Justiz-Vaillant et al., 2024). Itching usually worsens at night, causing sleep deprivation, which is suspected to be associated with a higher incidence of attention deficit hyperactivity disorder (ADHD), depression, and anxiety disorders in children with the condition (Wollenberg et al., 2023). AD often begins in early infancy. It is the first component of the 'atopic march' theory, which posits that atopic diseases occur in a specific sequence, beginning with atopic dermatitis (AD) and food allergies in infants, followed by bronchial asthma and allergic rhinitis (AR) in childhood. The etiology is heterogenic. Environmental and genetic factors play a significant role in developing the disease in the individual (Yang et al., 2020).

The basis of therapy, regardless of the severity of the condition, consists of hydrophilic topical preparations containing essential epidermal lipids and emollients. They aim to restore the hydro-lipid skin barrier and reduce transdermal water evaporation. Proper topical treatment can result in a diminished need for glucocorticoid use. Glucocorticoids are the main topical anti-inflammatory agents. Their application is required when the topical skin barrier-regaining interventions are insufficient or in flare-ups but only for a short period regarding side effects such as skin atrophy. If symptoms are severe, systemic treatment might be necessary. Systemic glucocorticoids, biological agents, and JAK inhibitors, either separately or in combination, can serve this purpose (Wollenberg et al., 2023).

AD is a significant burden to the health care system and the patient. A chronically disturbed sleeping cycle affects children psychologically. There is an increased risk of suicide in AD patients Wollenberg et al., (2023) and it shows how important it is to investigate new pathways that could relieve their suffering. Lemoine et al., (2023) investigated if the enrichment of infant's formula in probiotics exerted an influence on atopic disease prevalence and revealed that formulas with added probiotics (*Bifidobacterium lactis* Bb-

12, *Bifidobacterium animalis* sp., *Bifidobacterium lactis* HN019, *Lactobacillus fermentum* CECT5716 and *Lactobacillus rhamnosus* (LGG)) ameliorated AD in children. In Xue et al., (2023) reviewed articles regarding the efficacy of probiotics in pediatric AD. They indicated that restoring healthy and diverse gut microbiota, according to the literature, could modulate and support immune development (Xue et al., 2023).

The authors mentioned the "gut-skin axis" theory, which suggests that exposure to bacterial antigens in the intestines has the potential to influence skin hyperresponsiveness and inflammation. This review demonstrated that single-strain probiotic treatment significantly improved the Scoring Atopic Dermatitis Index (SCORAD) value compared to the placebo and the multi-strain probiotic group. Recently, two systematic reviews on the use of Lactobacillus in atopic dermatitis (AD) treatment have been published, and their findings are consistent: Certain species are beneficial as add-on therapy for AD in children (Xie et al., 2023; Fijan et al., 2023). Xie et al., (2023) reviewed literature considering specific strains of Lactobacilli *(L. rhamnosus, L. acidophilus, L. plantarum, L. sakei, L. reuteri, L. salivarius, L. paracasei, L. casei, L. delbrueckii, L. fermentum*) and their effects on the clinical manifestations of AD. Based on their research, probiotics can prevent or treat AD, and when administered during the perinatal period, they can prevent AD.

However, recommendations cannot be based on scant evidence (Xie et al., 2023). More clinical studies focusing on single strains as adjuvant therapy are needed (Fijan et al., 2023). The matter of interest is also probiotics administration to a woman during pregnancy or lactation and its influence on the risk of developing AD in their offspring. Colquitt et al., (2022) reviewed randomized controlled trials regarding mothers who received any probiotic while pregnant or during pregnancy and lactation. They concluded that probiotic supplementation in both cases could distinctly reduce the risk of infant AD or eczema (Table 4). The protective effect was more pronounced in children with a genetic predisposition to allergic diseases (Colquitt et al., 2022).

**Table 4** Probiotics supplementation in the prevention and treatment of atopic dermatitis

| Study | Year | Intervention | Conclusions |
|---|---|---|---|
| Colquitt et al., | 2022 | Any probiotic suplementation in mothers during the pregnancy or pregnancy and lactation | Distinctly reduced risk of infant AD or eczema in both cases |
| Lemoine et al., | 2023 | Enrichment of infant's formula in probiotics (Bifidobacterium lactis Bb-12, Bifidobacterium animalis sp., Bifidobacterium lactis HN019, Lactobacillus fermentum CECT5716 and Lactobacillus rhamnosus (LGG) | Ameliorated AD symptoms |
| Xue et al., | 2023 | Probiotics suplementation in pediatric AD | Single-strain probiotic treatment significantly improved the Scoring Atopic Dermatitis Index (SCORAD) value compared to the placebo and the multi-strain probiotic group |
| Xie et al., | 2023 | Specific strains of Lactobacilli supplementation (L. rhamnosus, L. acidophilus, L. plantarum, L. sakei, L. reuteri, L. salivarius, L. paracasei, L. casei, L. delbrueckii, L. fermentum) | Probiotics can prevent or treat AD, and when administered during the perinatal period, they can prevent AD |
| Fijan et al., | 2023 | Single-strain probiotic lactobacilli supplementation | Certain species are promising adjuvant treatments for decreasing AD in children. |

**Food Allergy**

Immunoglobulin-E-mediated food allergy (FA) is another atopic disease and a component of the "atopic march" (Yang et al., 2020; Tsuge et al., 2021). Symptoms of the condition include abdominal pain, diarrhea, nausea, and vomiting, as well as less apparent manifestations such as respiratory disorders, arrhythmias, and hypotension (Justiz-Vaillant et al., 2024). The risk of FA development is six times higher in children already suffering from AD than in ones without it. Research has shown that sensitization to food allergens can occur by epicutaneous exposure and that early anti-inflammatory intervention in infants with AD lowered FA prevalence. Also, the

probability of developing allergic asthma and AR is higher in children with FA. Allergic diseases are associated and having one increases the risk of having another.

Therefore, it is vital to find and introduce early strategies that could limit the progress of the atopic march (Tsuge et al., 2021). The increased prevalence of atopic diseases, including food allergies, over the past two decades, has prompted scientists to investigate contributing factors. The infant's diet appeared to be an interesting issue. The first assumption said that hypersensitization of the intestinal mucosa in atopy-susceptible children might be due to the early introduction of certain foods like eggs, cow's milk or peanuts. However, studies have shown otherwise. Early introduction of potential allergens appeared to exert a protective impact on FA development (Fijan et al., 2023). Intestinal microbiota, especially in the first months of life, has a significant influence on gaining mucosal immunotolerance and an effective intestinal barrier.

Furthermore, its disruption, as a consequence of cesarean section delivery, lack of breastfeeding, and early infancy antibiotics administration, may lead to hyperresponsiveness and excessive release of pro-inflammatory agents, resulting in food allergy. Therefore, it is worthwhile to investigate if the probiotics supplementation promoting robust and diverse gut microbiota could decrease the prevalence of FA or contribute to symptom alleviation (Nance et al., 2020). Investigations regarding the probiotics' influence on food allergy prevention when administered during pregnancy, breastfeeding, and to infants demonstrated that the reduction of risk of developing food sensitization was observed only in the case of maternal supplementation during pregnancy and continuing probiotics supplementation in infants (Nance et al., 2020).

In Berni-Canani et al., (2017) performed a 3-year randomized controlled trial following the results of extensively hydrolyzed casein formula (EHCF), with (group 1) or without LGG (group 2), administration to children with IgE-mediated cow milk allergy. They concluded that EHCF with LGG reduced the occurrence of other allergic manifestations and shortened the time of acquiring oral tolerance (Berni-Canani et al., 2017). As FA is an early atopic manifestation the dependence of the type of infants' formula and the first allergy symptoms development became a field of research. In a 36-month prospective cohort study, 365 children with cow's milk allergy were divided into cohorts receiving different formulas: EHCF + LGG formula, rice hydrolyzed formula, soy formula, extensively hydrolyzed whey formula, or amino acid-based formula.

The authors evaluated the effect of this intervention on atopic manifestation and immuno-tolerance acquisition. They revealed that the frequency of atopic manifestation was significantly lower in the EHCF + LGG group compared to other groups (Nocerino et al., 2021). The 2020 review focused on the role of the microbiome in FA and raised the subject of prebiotic use (Nance et al., 2020). The prebiotic definition was first introduced in 1995 by Glenn Gibson and Marcel Roberfroid and stated that it is "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and, or activity of one or a limited number of bacteria in the colon, and thus improves host health". The definition was updated in 2008 by International Scientific Association of Probiotics and Prebiotics to "a selectively fermented ingredient that results in specific changes in the composition and, or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health".

We can distinguish types of probiotics such as fructans, galacto-oligosaccharides, starch, glucose-derived oligosaccharides, and other oligosaccharides (Davani-Davari et al., 2019). The authors of the review reported that based on the literature searched, prebiotic supplementation in infants did not decrease the risk of developing FA, indicating a need for further research in this area (Nance et al., 2020). Oral immunotherapy (OIT) is a potential treatment method for food allergy (FA), aiming to induce tolerance to allergenic food through gradually escalating doses (Wood, 2017). Hsiao et al., (2017) conducted a randomized trial of combined probiotic and peanut oral immunotherapy (PPOIT).

In the primary outcome, their research has shown that after discontinuation of POIT treatment, 82.1% of the PPOIT group and 3.6% in the POIT + placebo group achieved sustained 2-week unresponsiveness. The follow-up study, four years after the end of POIT treatment, revealed that 67% (16 of 24) participants from the PPOIT group were more likely to continue eating peanuts compared to 4% (1 of 24) of the placebo group (Table 5). Authors suggested that PPOIT was associated with inducing long-lasting immunotolerance in peanut FA patients (Hsiao et al., 2017).

**Table 5** Probiotic and prebiotic supplementation in food allergy

| Study | Year | Type of study | Intervention | Conclusion |
|---|---|---|---|---|
| Berni-Canani et al., | 2017 | Randomized controlled trial | Administration of extensively hydrolyzed casein formula (EHCF), with (group 1) or without LGG (group 2) to children with IgE-mediated cow milk allergy | EHCF with LGG reduced the occurrence of other allergic manifestations and shortened the time of acquiring oral tolerance |
| Hsiao et al., | 2017 | Randomised, double-blind, placebo-controlled trial | Combined probiotic and peanut oral immunotherapy (PPOIT) | The primary outcome: After discontinuation of POIT treatment, 82.1% of the PPOIT group and 3.6% in the POIT + placebo group achieved sustained 2-week unresponsiveness. The follow-up study: Four years after the end of POIT treatment 67% participants from the PPOIT group were more likely to continue eating peanuts compared to 4% of the placebo group |
| Nance et al., | 2020 | Review | Probiotics administered during pregnancy, breastfeeding, and to infants | Reduction of risk of developing food sensitization observed only in the case of maternal supplementation during pregnancy and continuing probiotics supplementation in infants |
| Nance et al., | 2020 | Review | Prebiotic supplementation in infants | Prebiotic supplementation did not decrease the risk of developing FA |
| Nocerino et al., | 2021 | Cohort Study | Administration of different formulas to children with cow's milk allergy: EHCF + LGG formula, rice hydrolyzed formula, soy formula, extensively hydrolyzed whey formula, or amino acid-based formula | Frequency of atopic manifestation was significantly lower in the EHCF + LGG group compared to other groups |

As the prevalence of atopic diseases is increasing worldwide Fiuza et al., (2021), Wang et al., (2019), researchers are making an effort to provide new methods and means to aid the patients and unburden the healthcare system. According to the connection between intestinal microbiota composition and the development of immunotolerance Wang et al., (2019), probiotics use in immunological disorders became worth considering. The great advantage of probiotics is that they are considered safe. Thus, administrating them to the patients during trials entails low risk of adverse events (Depoorter and Vandenplas, 2021; Wang et al., 2019). Nevertheless, there are reports of endocarditis in patients with structural heart disease, bacteremia, pneumonia, or urosepsis (Wang et al., 2019).

Therefore, participants should be carefully selected to avoid putting vulnerable children at risk. In vitro and animal model studies' initial reports were optimistic (Mennini et al., 2017; Hufnagl et al., 2020). However, the findings of clinical trials appeared inconsistent. Authors highlight that there is a need for more thoroughly designed studies regarding single probiotic strains in specific diseases, the dosage, period, and route of administration (Wang et al., 2019; Colquitt et al., 2022; Lemoine et al., 2023; D'Elios et al., 2020). While research yields promising outcomes, it is inappropriate to make recommendations based solely on these findings without robust and repeatable evidence.

We would like to point out that to decrease the prevalence of allergic diseases, apart from making an effort to enrich the microbiome with probiotics use, we should take caution about modifiable risk factors and, therefore, avoid actions that diminish the biodiversity of intestinal microbiota, like antibiotics administration in early infancy, and pay attention to ordering them non-excessively, but when indicated and needed. We should educate patients about the impact of delivery methods and breastfeeding on the development of allergic diseases in children. These factors significantly influence the composition of gut and skin microbiota, thereby, affecting susceptibility to atopic diseases, especially in predisposed individuals (Hufnagl et al., 2020; Colquitt et al., 2022).

## 4. CONCLUSIONS

Despite promising outcomes of numerous studies regarding probiotics use in allergic diseases, there are reports of finding no significant difference. In conclusion, probiotics have the potential to become safe and well-tolerated add-on therapy in atopic diseases. However, there is still too little evidence to make any recommendations for their routine use.

**Authors' Contributions**

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**Informed consent**

Not applicable.

**Ethical approval**

Not applicable.

**Conflict of interest**

The authors declare that there is no conflict of interests.

**Data and materials availability**

All data sets collected during this study are available upon reasonable request from the corresponding author.

## REFERENCES


1. Ahmed M, Billoo AG, Iqbal K. Efficacy of probiotic in perennial allergic rhinitis under five-year children: A randomized controlled trial. Pak J Med Sci 2019; 35(6):1538-1543. doi: 10.12669/pjms.35.6.744
2. Anania C, Di-Marino VP, Olivero F, De-Canditiis, Brindisi G, Iannilli F, De-Castro G, Zicari AM, Duse M. Treatment with a Probiotic Mixture Containing Bifidobacterium animalis Subsp. Lactis BB12 and Enterococcus faecium L3 for the Prevention of Allergic Rhinitis Symptoms in Children: A Randomized Controlled Trial. Nutrients 2021; 13(4):1315. doi: 10.3390/nu13041315
3. Beasley R, Harrison T, Peterson S, Gustafson P, Hamblin A, Bengtsson T, Fagerås M. Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients with Poorly Controlled Asthma: A Systematic Review and Meta-analysis. JAMA Netw Open 2022; 5(3):e220615. doi: 10.1001/jamanetworkopen.2022.0615. Erratum in: JAMA Netw Open 2022; 5(5):e2216068. doi: 10.1001/jamanetworkopen.2022.16068
4. Berni-Canani R, Di-Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di-Scala C, Granata V, Nocerino R. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. J Allergy Clin Immunol 2017; 139(6):1906-1913.e4. doi: 10.1016/j.jaci.2016.10.050
5. Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, Leong R, Boushey HA, Hilton JF. Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial. Pediatrics 2017; 140(3):e20163000. doi: 10.1542/peds.2016-3000
6. Capponi M, Gori A, De-Castro G, Ciprandi G, Anania C, Brindisi G, Tosca M, Cinicola BL, Salvatori A, Loffredo L, Spalice A, Zicari AM. (R)Evolution in Allergic Rhinitis Add-On Therapy: From Probiotics to Postbiotics and Parabiotics. J Clin Med 2022; 11(17):5154. doi: 10.3390/jcm11175154
7. Chabra R, Gupta M. Allergic and Environmentally Induced Asthma. StatPearls [Internet], 2023.
8. Ciprandi G, Tosca MA. Probiotics in Children with Asthma. Children (Basel) 2022; 9(7):978. doi: 10.3390/children9070978
9. Colquitt AS, Miles EA, Calder PC. Do Probiotics in Pregnancy Reduce Allergies and Asthma in Infancy and Childhood? A Systematic Review. Nutrients 2022; 14(9):1852. doi: 10.3390/nu14091852
10. D'Elios S, Trambusti I, Verduci E, Ferrante G, Rosati S, Marseglia GL, Drago L, Peroni DG. Probiotics in the prevention and treatment of atopic dermatitis. Pediatr Allergy Immunol 2020; 31 Suppl 26:43–5. doi: 10.1111/pai.13364
11. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, Berenjian A, Ghasemi Y. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods 2019; 8(3):92. doi: 10.3390/foods8030092
12. Depoorter L, Vandenplas Y. Probiotics in Pediatrics. A Review and Practical Guide. Nutrients 2021; 13(7):2176. doi: 10.3390/nu13072176
13. Drago L, Cioffi L, Giuliano M, Pane M, Amoruso A, Schiavetti I, Reid G, Ciprandi G, PROPAM Study Group. The Probiotics in Pediatric Asthma Management (PROPAM) Study in the Primary Care Setting: A Randomized, Controlled, Double-Blind Trial with *Ligilactobacillus salivarius* LS01 (DSM 22775) and *Bifidobacterium breve* B632 (DSM 24706). J Immunol Res 2022; 2022:e3837418. doi: 10.1155/2022/3837418
14. Fijan S, Kolč N, Hrašovec M, Jamtvedt G, Pogačar MŠ, Mičetić Turk D, Maver U. Single-Strain Probiotic Lactobacilli for the Treatment of Atopic Dermatitis in Children: A Systematic Review and Meta-Analysis. Pharmaceutics 2023; 15(4):1256 doi: 10.3390/pharmaceutics15041256
15. Fiuza BSD, Fonseca HF, Meirelles PM, Marques CR, Da-Silva TM, Figueiredo CA. Understanding Asthma and Allergies by the Lens of Biodiversity and Epigenetic Changes. Front Immunol 2021; 12:623737. doi: 10.3389/fimmu.2021.623737
16. Garn H, Potaczek DP, Pfefferle PI. The Hygiene Hypothesis and New Perspectives-Current Challenges Meeting an Old Postulate. Front Immunol 2021; 12:637087. doi: 10.3389/fimmu.2021.637087
17. Haahtela T. A biodiversity hypothesis. Allergy 2019; 74(8):1445–1456. doi: 10.1111/all.13763
18. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK, Burks W, Donath S, Orsini F, Tey D, Robinson M, Su EL. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomized, double-blind, placebo-controlled trial. Lancet Child Adolesc Health 2017; 1(2):97–105. doi: 10.1

016/S2352-4642(17)30041-X. Erratum in: Lancet Child Adolesc Health 2017; 1(3):e2. doi: 10.1016/S2352-4642(17)30099-8

19. Huang CF, Chie WC, Wang IJ. Efficacy of Lactobacillus Administration in School-Age Children with Asthma: A Randomized, Placebo-Controlled Trial. Nutrients 2018; 10(11) :1678. doi: 10.3390/nu10111678
20. Hufnagl K, Pali-Schöll I, Roth-Walter F, Jensen-Jarolim E. Dysbiosis of the gut and lung microbiome has a role in asthma. Semin Immunopathol 2020; 42(1):75–93. doi: 10.1007/s00281-019-00775-y
21. Justiz-Vaillant AA, Modi P, Jan A. Atopy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
22. Kang MG, Han SW, Kang HR, Hong SJ, Kim DH, Choi JH. Probiotic NVP-1703 Alleviates Allergic Rhinitis by Inducing IL-10 Expression: A Four-week Clinical Trial. Nutrients 2020; 12(5):1427. doi: 10.3390/nu12051427
23. Lemoine A, Tounian P, Adel-Patient K, Thomas M. Pre-, pro-, syn-, and Postbiotics in Infant Formulas: What Are the Immune Benefits for Infants? Nutrients 2023; 15(5):1231. doi: 10.3390/nu15051231
24. Liu P, Hu T, Kang C, Liu J, Zhang J, Ran H, Zeng X, Qiu S. Research Advances in the Treatment of Allergic Rhinitis by Probiotics. J Asthma Allergy 2022; 15:1413–1428. doi: 10.2147/JAA.S382978
25. Maciag MC, Phipatanakul W. Prevention of Asthma: Targets for Intervention. Chest 2020; 158(3):913–22. doi: 10.1016/j.chest.2020.04.011
26. Mennini M, Dahdah L, Artesani MC, Fiocchi A, Martelli A. Probiotics in Asthma and Allergy Prevention. Front Pediatr 2017; 5:165. doi: 10.3389/fped.2017.00165
27. Miraglia-Del-Giudice M, Indolfi C, Capasso M, Maiello N, Decimo F, Ciprandi G. Bifidobacterium mixture (B longum BB536, B infantis M-63, B breve M-16V) treatment in children with seasonal allergic rhinitis and intermittent asthma. Ital J Pediatr 2017; 43(1):25. doi: 10.1186/s13052-017-0340-5
28. Nance CL, Deniskin R, Diaz VC, Paul M, Anvari S, Anagnostou A. The Role of the Microbiome in Food Allergy: A Review. Children (Basel) 2020; 7(6):50. doi: 10.3390/children7060050
29. Nocerino R, Bedogni G, Carucci L, Cosenza L, Cozzolino T, Paparo L, Palazzo S, Riva L, Verduci E, Berni-Canani R. The Impact of Formula Choice for the Management of Pediatric Cow's Milk Allergy on the Occurrence of Other Allergic Manifestations: The Atopic March Cohort Study. J Pediatr 2021; 232:183-191.e3. doi: 10.1016/j.jpeds.2021.01.059
30. Pfefferle PI, Keber CU, Cohen RM, Garn H. The Hygiene Hypothesis – Learning from but Not Living in the Past. Front Immunol 2021; 12:635935. doi: 10.3389/fimmu.2021.635935
31. Tsuge M, Ikeda M, Matsumoto N, Yorifuji T, Tsukahara H. Current Insights into Atopic March. Children (Basel) 2021; 8 (11):1067. doi: 10.3390/children8111067
32. Von-Mutius E. The "Hygiene Hypothesis" and the Lessons Learnt from Farm Studies. Front Immunol 2021; 12:635522. doi: 10.3389/fimmu.2021.635522
33. Wang HT, Anvari S, Anagnostou K. The Role of Probiotics in Preventing Allergic Disease. Children 2019; 6(2):24. doi: 10.3390/children6020024
34. Wise SK, Damask C, Roland LT, Ebert C, Levy JM, Lin S, Luong A, Rodriguez K, Sedaghat AR, Toskala E, Villwock J, Abdullah B, Akdis C, Alt JA, Ansotegui IJ, Azar A, Baroody F, Benninger MS, Bernstein J, Brook C, Campbell R, Casale T, Chaaban MR, Chew FT, Chambliss J, Cianferoni A, Custovic A, Davis EM, DelGaudio JM, Ellis AK, Flanagan C, Wytske J. Fokkens WJ, Franzese C, Greenhawt M, Gill A, Halderman A, Hohlfeld JM, Incorvaia C, Joe SA, Joshi S, Kuruvilla ME, Kim J, Klein AM, Krouse HJ, Kuan EC, Lang D, Larenas-Linnemann D, Laury AM, Lechner M, Lee SE, Lee VS, Loftus P, Marcus S, Marzouk H, Mattos J, McCoul E, Melen E, Mims JW, Mullol J, Nayak JV, Oppenheimer J, Orlandi RR, Phillips K, Platt M, Ramanathan M, Raymond M, Rhee C, Reitsma S, Ryan M, Sastre J, Schlosser RJ, Schuman TA, Shaker MS, Sheikh A, Smith KA, Soyka MB, Takashima M, Tang M, Tantilipikorn P, Taw MB, Tversky J, Tyler MA, Veling MC, Wallace D, Wang DY, White A, Zhang L. International consensus statement on allergy and rhinology: Allergic rhinitis – 2023. Int Forum Allergy Rhinol 2023; 13:293–859. doi: 10.1002/alr.23090
35. Wollenberg A, Werfel T, Ring J, Ott H, Gieler U, Weidinger S. Atopic Dermatitis in Children and Adults—Diagnosis and Treatment. Dtsch Arzteblatt Int 2023; 120(13):224–234. doi: 10.3238/arztebl.m2023.0011
36. Wood R. Oral Immunotherapy for Food Allergy. J Investig Allergol Clin Immunol 2017; 27(3):151–159. doi: 10.18176/jiaci.0143
37. Xie A, Chen A, Chen Y, Luo Z, Jiang S, Chen D, Yu R. Lactobacillus for the treatment and prevention of atopic dermatitis: Clinical and experimental evidence. Front Cell Infect Microbiol 2023; 13:1137275. doi: 10.3389/fcimb.2023.1137275
38. Xue X, Yang X, Shi X, Deng Z. Efficacy of probiotics in pediatric atopic dermatitis: A systematic review and meta-

analysis. Clin Transl Allergy 2023; 13(7):e12283. doi: 10.1002/clt2.12283

39. Yamashita M, Miyoshi M, Iwai M, Takeda R, Ono T, Kabuki T. Lactobacillus helveticus SBT2171 Alleviates Perennial Allergic Rhinitis in Japanese Adults by Suppressing Eosinophils: A Randomized, Double-Blind, Placebo-Controlled Study. Nutrients 2020; 12(12):3620. doi: 10.3390/nu12123620
40. Yang L, Fu J, Zhou Y. Research Progress in Atopic March. Front Immunol 2020; 11:1907. doi: 10.3389/fimmu.2020.01907